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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/993,748
Filing Date: November 14, 2001
Appellant(s): ASHKENAZI ET AL.

Barrie Greene
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/10/05.

500.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: the rejection of claims 119-127 and 129-131 under 35 USC 102(b) has been withdrawn in view of the fact that this Baker et al. reference is Appellants' own work.

(7) Grouping of Claims

The rejection of claims 119-127 and 129-131 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Skolnick, J. et al "From genes to protein structure and function:novel applications of computational approaches in the genomic era." Trends in Biotech, vol 18, no. 1 (2000), pp. 34-39

Bork, P. "Powers and pitfalls in sequence analysis:the 70% hurdle." Genome Research, vol. 10 (2000), pp. 398-400.

Doerks, T, et al. "Protein annotation:detective work for function prediction." Trends in Genetics, vol 14, No. 6 (June 1998), pp. 248-250.

Smith, TF, et al. "The challenges of genome sequence annontation or "the devil is in the details." Nature Biotechnology, vol. 15 (November 1997), p. 1222-1223.

Brenner, SE. "Errors in genome annotation." Trends in Genetics, vol. 15, No. 4 (April 1999), p. 132.

Bork, P. et al. "Go hunting in sequence databases but watch out for the traps." Trends in Genetics, vol. 12, No. 10 (October 1996), pp. 425-427.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 119-127 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility. These claims are directed to polypeptides having various sequence homology to SEQ ID NO:314. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

At paragraph #8 of the Declaration, Dr. Fong states "[t]he MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can

boost the immune system to respond to a particular antigen that may not have been immunologically active previously". This is not what the instant specification asserts at pages 204-206. There is no mention in the instant specification about boosting the immune system "to respond to a particular antigen that may not have been immunologically active previously". It would appear that Dr. Fong is reading the results of the Peterson et al. reference into the disclosure of the instant specification. However, the Peterson et al. reference was not available at the time the instant application was filed, therefore, reliance on the methods and results of this reference is improper.

In paragraph #9 of the Declaration, Dr. Fong states that IL-12 was first identified in an MLR in Gubler et al. (PNAS 88: 4143-4147, 1991). However, a review of Gubler et al. does not reveal the use of MLR in evaluating the biological effects of IL-12. Gubler et al. teach that IL-12 is produced by peripheral blood lymphocytes (predominantly B cells) under appropriate conditions and that IL-12 activates NK cells, facilitates the generation of specific allogeneic CTL responses and stimulates secretion of gamma-interferon. Additionally, IL-12 synergizes with IL-2 to cause the proliferation of resting peripheral blood lymphocytes. Therefore, the further work of researchers regarding IL-12 was not based on the results of a single assay, being the MLR, but rather by a body of work which provides for a number of biological activities of IL-12 which are not disclosed for the claimed invention. The claimed invention is not IL-12. Secondly, the methods of Peterson et al. are not disclosed in the instant specification and are after the filing date of the instant application.

In paragraph 10 of the Declaration, Dr. Fong asserts "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12". This is an assertion not supported by any facts or evidence of record. First, the instant specification fails to disclose the degree of activity for the claimed invention in the MLR assay. The specification states that any positive increase over control is considered positive. Therefore, there is no disclosure that the activity in the assay was at least 180%. Secondly, there is no evidence of record which correlates an activity of at least 180% of control as predictive of an activity of IL-12. It is not clear from what data this conclusion is derived. Therefore, the Declaration is not persuasive to overcome the holding of a lack of utility for the claimed invention based on the MLR assay.

Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 119-127 and 129-131 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

B. Furthermore, even if the claims possessed utility under 35 USC 101, claims 119-127 and 129-131 would still be rejected under 35 USC 112, first paragraph, because the specification, while then being enabling for SEQ ID NO:313 and 314, does not reasonably provide enablement for polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:314, to the protein encoded by ATCC No. 203128, for the extracellular domain thereof, or for fusion proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Applicants have added the limitation that the polypeptides are immunostimulants and now the claims are defined both structurally and functionally. However, the claims encompass an unreasonable number of inoperative polypeptides, or polynucleotides which encode these polypeptides, which the skilled artisan would not know how to use.

There are no working examples of polynucleotides or polypeptides less than 100% identical to SEQ ID NO:313 or 314, or the mature form thereof (i.e. lacking its signal peptide). The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed a specific function disclosed in the instant specification, in which there is none. While the specification generally describes homologous proteins, Applicants still have not taught to which family of proteins the protein of the present invention belongs. The specification does not provide guidance for using polynucleotides encoding polypeptides related to (*i.e.*, 80%-99% identity) but not identical to SEQ ID NO:313 or 314 which do not have any specific, known function. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of proteases and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO:314, the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO:314, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

(11) Response to Argument

Claim Rejections - 35 USC § 101

Appellants argue on page 10 of the Appeal Brief that the case law cited on pages 8-10 of the Brief demonstrates that the invention complies with the utility guidelines under 35 USC 101. This argument has been considered, but is not deemed persuasive. In *Brenner v. Manson* the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

To this effect, Appellants argue on page 9 that "In general, Applicant's assertion of utility creates a presumption of utility...unless there is a reason...to question [its] utility or scope." Appellants also argue on pages 10-11 of the Brief that "rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility. This argument has been considered, but is not deemed persuasive. That section of the MPEP (2170.01) also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101."

Appellants also argue on pages 5-6 and 11-12 of the Appeal Brief that the protein of the present invention, PRO1346 (SEQ ID NO:314) is positive in the MLR assay, which is a well-established assay for evaluating test compounds for their ability to stimulate T-lymphocyte stimulation in vitro and compounds which can stimulate T-cell proliferation are beneficial in immune disorders. Appellants also argue that the Declaration of Dr. Fong states "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant" (i.e. in vivo).

These arguments have been considered, but are not deemed persuasive for the reasons already of record on pages 3-4 of the Office Action mailed 11/5/05 as well as for the following reasons. It can be concluded that Appellants major argument is that the MLR assay is predictive of in vivo effects, such as treating cancers, HIV/AIDS and certain other viral infections (top of page 13 of the Brief) since T-cells (whose activity is measured, whether directly of indirectly by MLR) have long been known to be

involved in these diseases (first two paragraphs of page 13 of the Brief). Appellants argue on page 8 of the Brief that, according to the MPEP (2107.03), if the in vitro data is "reasonably correlated" to a particular pharmacological or therapeutic utility" the data can be sufficient to establish therapeutic or pharmacological utility.

In light of these arguments, the major question raised by the Examiner is whether or not MLR is, in fact, predictive of in vivo therapeutic effects. It should be noted that nowhere in the case law, or prior art cited by Appellants, that in vitro pharmacological data is indicative of in vivo efficacy. Terms such as "may correlate" are used. Appellants are using data from one assay, MLR, and concluding that, based on a positive result in this assay, the compounds tested would be expected to treat diseases such as cancers, HIV/AIDS and other viral infections. On page 10 of the Brief, Appellants argue that this in vitro data "consequently [can be used] for assessing the immune response of an individual." However, in light of the Appellants' arguments and the fact that only one example of a compound (IL-12) showed promise in treating one disease (melanoma) and, respectfully, just so happened to be positive in one specific assay (discussed below), the Examiner concludes that the MLR data in not "reasonably correlated" to the described methods of treating such diseases. Appellants, respectfully, have provided a bold assertion of the correlation between in vitro and in vivo results. There is nothing in the literature which provides such a conclusion, only the possibility that a correlation may exist.

Cancer treatment is a complex issue, as is treating HIV/AIDS as is evident from the fact that treatment is not always successful, or different treatment regimens are usually required. It would, therefore, lead the artisan to believe that treatment of such complex diseases would require more than just activating dendritic cells or T-cells, as is performed in the MLR assay. If, respectfully, the mechanism of action of these diseases was that simple and the MLR assay was so well-known and reliable at the time of the present invention as to be able to predict in vivo results from a positive in vitro test then all cancers, HIV/AIDS, viral infections, or any other disease which would benefit from increased T-cell production or stimulation, as is the basis for MLR, would have been treated/cured. This issue is further discussed in the rejection under 35 USC 112, first paragraph, below. Therefore, in contrast to Appellants' arguments on page 9 of the Brief, the Examiner has established "that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility." This argument is further strengthened by Appellants' argument in the first paragraph on page 9 of the Brief that one utility under 35 USC 101 can be questioned based on the "objective truth of the statement utility **or its scope**." Clearly, Appellants have not provided sufficient information as to how to practice the scope of the invention (i.e. treating all

cancers, HIV/AIDS, etc). Therefore, "the claims of usefulness are not believable on their face" (page 9, first paragraph, of the Brief).

Treating such complex and general diseases such as cancer is, again, a complex issue. The use of the MLR assay to predict the effect that one compound would have in such a complex in vivo situation is difficult as numerous factors would be expected to play a role in the progression of these diseases, or else diseases such as cancer, HIV/AIDS, etc. would all be easily treated using identical methods. This situation can be compared to one such as a heart attack (representing here a cure for cancer). It is well-known that factors such as cigarette smoking, high cholesterol, diet, exercise, stress, genetic, high blood pressure, drinking alcohol and overall lifestyle (each one analogous to the MLR assay) can all play a role in a heart attack. Using the MLR assay to conclude that one can treat cancer is, respectfully, similar to saying that quitting smoking, or a compound which reduces cholesterol can prevent heart attacks. It would be expected that people smoke or drink to reduce stress. Again, both smoking and stress are well-known factors in heart attacks. Therefore, just because smoking (a factor) reduces stress (another factor) does not mean that smoking can prevent heart attacks. The conclusion drawn from this is that one must be extremely careful in extrapolating the data from one experiment to make conclusions for a complex, multi-faceted disease state.

In paragraph 10 of the Declaration (restated on pages 11, 12 and 19 of the Brief) , Dr. Fong asserts:

> it is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant.

As argued on pages 3-4 of the Office Action mailed 11/5/04, this is an assertion not supported by any facts or evidence of record. First, the instant specification fails to disclose the degree of activity for the claimed invention in the MLR assay. The specification states that any positive increase over control is considered positive. Therefore, there is no disclosure that the activity in the assay was at least 180%, *only that this activity is preferred.* There is no data showing that PRO1346, in fact, has activity 180% of control. Therefore, given the fact that no data regarding percent above control is given for PRO1346 and that the Declaration does not show an amount above control for PRO1346, the Examiner would have, contrary to Appellants' arguments, reason to doubt this assertion. Secondly, there is no evidence of record which correlates an activity of at least 180% of control as predictive of an activity of IL-12. It is not clear from what data this conclusion is derived. Therefore, the Declaration is not

persuasive to overcome the holding of a lack of utility for the claimed invention based on the MLR assay. Respectfully, on page 11 of the Brief, instead of providing a simple, clear conclusion without hesitation that PRO1346 does have an activity at least 180% of control, Appellants provide case law and arguments which detract from the specific issue at hand.

On page 15 of the Brief, Appellants argue that the Examiner is incorrect and that, according to the Fong Declaration, the only remaining cells to be used in the MLR assay were dendritic cells (DC) and that the function of these cells was well-known. Similarly, their use in melanoma was also well-known. These arguments have been considered, but are not deemed persuasive. First, there appears to be a discrepancy in what Dr. Fong has stated on page 12 and what Appellants have stated on page 16 (underlined). On page 16, Appellants state:

> Thus one of skill in the art would have understood at the time of filing that (i) molecules which enhanced the proliferation of stimulated T-cells would increase the ability of DCs to convert antigens to immunogens...

whereas the Fong Declaration states that the MLR assay of the present invention:

> is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the ' MLR, and thus identifies immume stimulants that can boost the immume system to respond to a particular antigen that may not have been immumologically active previously. (Parapaph 8 of the Fong Declaration.)

The question this raises is what appears to be a contradiction in the relationship between DCs and T-cells. Appellants state that molecules which enhance T-cell proliferation would then affect DCs, whereas Dr. Fong states that DCs drive T-cells. In other words, the order of T-cell and DC activation is reversed in these two statements. Second, it appears that the examples given in the Brief include the use of the MLR assay for diseases such as infections, HIV and melanoma (paragraph bridging pages 4-5). Appellants have given the impression that this assay is well-known in the art to find compounds to treat these types of diseases; however, it appears that the only disease actually studied is melanoma. Therefore, in contrast to Appellants' arguments that this assay can be used to find immunostimulants for a host of diseases, the only provide melanoma as an example. This specific teaching is not disclosed in the specification. While it may be true, as emphasized by Dr. Fong on page 12 of the Brief, that

"immunostimulants are important and highly desirable" this, in itself, does not provide a specific or substantial use for the present invention.

On page 16 of the Brief, Appellants further argue that Gubler teach the use of an assay similar to the MLR assay. However, the Gubler assay uses lymphoblasts whereas the MLR assay uses dendritic cells. Furthermore, differences include the discussion in Gubler of IL-12 synergizing with IL-2 (pages 16-17 of the Brief) whereas the present invention focuses on IL-12 for its standard for PRO1346. Synergizing IL-2 is not pertinent to the present issue. IL-2 may, itself, be well-known in the treatment of cancer. In the present invention, there is no requirement for synergizing with another compound which may already be known to aid in the treatment of diseases. Regardless, the conclusion drawn by Appellants is that in vitro activity is predictive of in vivo efficacy (page 18 of the Brief). However, nowhere in Gubler is this demonstrated, nor is it concluded that in vitro results can be extrapolated to in vivo efficacy. Gubler only states that their compound *might* have an effect in vivo (page 17 of the Brief):

> "and thus might have synergistic immunoenhancing effects when administered together with recombinant IL-2 in vivo ."

Therefore, in summary, the results of the MLR assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLR assay to correlate to a general stimulatory effect on the immune system. There is no teaching in the art or in the instant specification which would make this asserted utility readily available to the skilled artisan. The assay appears to merely assess the immune response of an individual to allogens.

Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Appellants argue that the protein of the present invention is enabled under 35 USC 112, first paragraph, since it possesses utility under 35 USC 101 as argued above. In addition to the fact that the present invention does not possess utility as seen above, the present invention is not enabled. One of ordinary skill in the art would not know how to use the protein of the present invention, or its variants, to treat any diseases, including, for example, melanoma or HIV, as argued by Appellants.

As discussed in the above rejection under 35 USC 101, cancer treatment is a complex issue, as is evident from the fact that treatment is not always successful, or different treatment regimens are usually

required. It would, therefore, lead the artisan to believe that treatment of such complex diseases would require more than just activating dendritic cells or T-cells, as is performed in the MLR assay. If, respectfully, the mechanism of action of these diseases was that simple and the MLR assay was so well-known and reliable at the time of the present invention as to be able to predict in vivo results from a positive in vitro test then all cancers, HIV/AIDS, viral infections, or any other disease which would benefit from increased T-cell production or stimulation, as is the basis for MLR, would have been treated/cured. Appellants have only provided evidence that one cancer, melanoma can be treated by certain compounds, such as IL-12, which was identified in an assay similar to, but different from, MLR. Therefore, the scope of treating any disease which involves T-cells is excessive in view of the lack of guidance and working examples of the use of PRO1346, or any compound identified by MLR, or *arguendo*, other than IL-12, to treat the entire scope of diseases affected by T-cells. Clearly, Appellants have not provided sufficient information as to how to practice the scope of the invention (i.e. treating all cancers, HIV/AIDS, etc).

Treating such complex and general diseases such as cancer is, again, a complex issue. The use of the MLR assay to predict the effect that one compound would have in such a complex in vivo situation is difficult as numerous factors would be expected to play a role in the progression of these diseases, or else diseases such as cancer, HIV/AIDS, etc. would all be easily treated using identical methods. In other words, it is not predictable to the artisan how to treat the myriad of diseases whose only common thread is T-cell involvement. This situation can be compared to one such as a heart attack (representing here a cure for cancer). It is well-known that factors such as cigarette smoking, high cholesterol, diet, exercise, stress, genetic, high blood pressure, drinking alcohol and overall lifestyle (each one analogous to the MLR assay) can all play a role in a heart attack. Using the MLR assay to conclude that one can treat cancer is, respectfully, similar to saying that quitting smoking, or a compound which reduces cholesterol can prevent heart attacks. It would be expected that people smoke or drink to reduce stress. Again, both smoking and stress are well-known factors in heart attacks. Therefore, just because smoking (a factor) reduces stress (another factor) does not mean that smoking can prevent heart attacks. The conclusion drawn from this is that one must be extremely careful in extrapolating the data from one experiment to make conclusions for a complex, multi-faceted disease state.

Therefore, due to the breadth of the invention which focuses on the use of the proteins of the present invention to treat a wide array of diseases from cancer to viral infections as well as the lack of, or at most, minimal, guidance and working examples of compounds testing positive in these assays which are used to treat such diseases along with the lack of predictability of how to use this assay as indicative

of, or the compounds identified in the assay as useful for, the treatment of such diseases, the Examiner holds that undue experimentation is required to practice the claimed invention.

B. Appellants further argue that the recitation of 80% identity is also enabled since the claims recite a functional limitation "is an immunostimulatnt" and that by following the disclosure the artisan would know how to test for this function. Appellants further argue that page 306 of the specification teaches how to determine percent identity and that pages 371-373 teach which regions of the protein are required for function, as well as an example. Appellants further argue that there may be polypeptides that stimulate the immune system through mechanisms unrelated to those of PRO1346, and thus do not resemble PRO1346 in structure. These structurally unrelated polypeptides, however, would not be encompassed by claims requiring at least 80% amino acid sequence identity to SEQ ID NO:314. Appellants claim only those proteins which meet both limitations of the claims, structural and functional. Given the structural limitation, the additional functional limitation clearly acts to further define the claimed genus.

These arguments have been considered, but are not deemed persuasive. Appellants have added a functional limitation. However, the breadth of the claims remains excessive since the functional limitation is general. Appellants have only demonstrated that the polypeptides are active in the MLR assay. As seen on page 2 (paragraph 8) of the Declaration under 37 CFR 1.132 by Dr. Fong, the MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR. This assay limits the polypeptides which can induce the proliferation of T-cells. The immune system comprises more than just T-cells. Since the claims are not limited to polypeptides which are shown to be immunostimulatory in the MLR assay, it includes in breadth the stimulation of the immune system by polypeptides which can stimulate the immune system in other ways, such as activation of B-cells. Appellants have not provided any guidance or working examples of polypeptides which can stimulate immune cells other than via the MLR, nor is it predictable which amino acids residues are required to stimulate any aspect of the immune system. Therefore, the artisan would not know which residues to alter and which to maintain in order to retain the functional activity of the protein. Appellants argue that pages 306 and 371-373 provide guidance regarding percent identity and which residues are required to maintain the functional characteristics of the wild-type protein. However, being able to identify proteins based on percent identity does not provide any information regarding the structure/function relationship of a protein. Furthermore,

the Examiner, respectfully, cannot find where on pages 371-373 any specific structure/function information for PRO1346 can be found, other than just general teachings of proteins in general.

Therefore, in summary, the breadth of the claims is excessive with regard to Applicants claiming polynucleotides encoding polypeptides which can act as immunostimulants by any means. Furthermore, Applicants have not provided any guidance or working examples of polypeptides which can stimulate immune cells other than via the MLR, nor is it predictable which amino acids residues are required to stimulate any aspect of the immune system. For these reasons, the Examiner maintains that undue experimentation would be required to practice the claimed invention.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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September 1, 2005

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